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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/477,097	06/07/95	LIVINGSTON	P	43016-B/JPW/

18M1/0711

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EXAMINER	
CAPUTA, A	
ART UNIT	**PAPER NUMBER**
1817	16

DATE MAILED: 07/11/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1-File Copy

PT -90C (REV. 2/95)

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

Office Action Summary	Application No. 08/477,097	Applicant(s) Livingston et al.
	Examiner Anthony C. Caputa	Group Art Unit 1817

☒ Responsive to communication(s) filed on *11/15/95; 12/13/96; 1/6/97; 4/21/97; and 5/5/97*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4, 6-20, and 44-52* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 6-20, and 44-52* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *15*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1817.

2. Applicants' request to Correct the Error in Filing Receipt dated November 13, 1995 was entered as Paper No. 10. Applicants' amendment dated December 10, 1997 was entered as Paper No. 11. Applicants' Supplemental Communication dated January 6, 1997 was entered as Paper No. 12. Applicants' Communication dated April 21, 1997 was entered as Paper No. 14. Applicants' Information Disclosure Statement and Corrected Filing Receipt dated May 2, 1997 was entered as Paper No. 15. Claims 1-4, 6-20, and 44-52 are pending.

Specification

3. The prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mailed 6/10/96 (see Paper No. 9).

Applicants submit they will submit a new Figure 6B to overcome the rejection when the case is in condition for allowance. Until applicants submit a proper Figure said objection is maintained.

Double Patenting

4. The prior provisional rejection of claims 1-20, and 44-52 under 35 U.S.C. 101 as claiming the same invention as that of claims 44-52 of copending Application No. 08/475,784 is withdrawn in view of applicants' amendment.

5. Claims 1-4, 6-20 and 44-52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-20 and

44-52 of copending Application No. 08/475,784. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and the copending application are both drawn to a vaccine comprising a ganglioside selected from the group consisting of GM2, GM3, GD2, GD3, GD3 lactone, O-acetyl GD3, and GT3, or oligosaccharide portion thereof conjugated to an immunogenic protein (i.e. KLH) thereof, with an adjuvant.

6. Claims 1-4, 6-20 and 44-52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44, and 46-56 of copending Application Nos. 08/477,147 and 08/481,809. Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the Office Action mailed 6/10/96 (see Paper No. 9).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants argue the provisional obviousness-type double patenting rejections (see Paper No. 14) should be withdrawn in view of applicants arguments under Sections 101, 112 and 103. Applicants arguments are not persuasive since applicants arguments under 112 and 103were not found to be persuasive for the reasons set forth below. Beyond this applicants arguments under 103 (or 112) are not persuasive to obviate the rejection since teachings as set forth under 103 (or 112) were not used in the provisionally rejected under the judicially created doctrine of obviousness-type double patenting. Applicants arguments under 101 are not persuasive to obviate the obviousness-type double patenting rejection because although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and the copending application are both drawn to a vaccine comprising a ganglioside selected from the group consisting of GM2, GM3, GD2, GD3, GD3

lactone, O-acetyl GD3, and GT3, or oligosaccharide portion thereof conjugated to an immunogenic protein (i.e. KLH) thereof, with an adjuvant.

The Examiner suggest applicants provide terminal disclaimers to obviate the obvious type double patenting rejection over the claimed invention of copending Application Nos. 08/475,784; 08/477,147; and 08/481,809.

Claim Rejections - 35 USC § 112

7. The prior rejection of claims 4, and 13-17 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicants' arguments.

8. Claims 1-4, 6-20 and 44-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed 6/10/96 (see Paper No. 9).

Applicants essentially argue the reference by Fung et al should not used to question whether antibodies against the ganglioside conjugate vaccines will prevent cancer since the experiments as set forth by Fung et al. were not used to study whether GM2-KLH conjugated vaccine prolonged survivability. Applicants further argue there is no evidence by Fung et al that the cancer cells express GM2, nor the antibodies to GM2 were generated after vaccination. Applicants arguments are not persuasive to obviate the rejection. Whether or not the objective of Fung et al experiments was to determine the efficacy of the GM2-KLH conjugated vaccine is not sufficient to overcome the rejection. As set forth previously since the production of high titers of antibodies in melanoma patients with the GM2-KLH does not appear to correlate with the prevention of cancer as exemplified by the teachings of Fung et al., it is unpredictable if the composition as claimed is efficacious as a vaccine. Beyond this applicants arguments are not

sufficient to obviate the rejection since the art as exemplified by Cohen et al. (see Science 262:841-843 especially page 843) states: "Cancer vaccines are highly experimental". Since the specification provide insufficient guidance of how to use the composition as a vaccine and the art at the time of the invention set forth cancer vaccines are highly experimental it is reasonable to conclude a skilled artisan would be forced into undue experimentation to practice the claimed invention.

Applicants' amendment is sufficient to obviate the objection to the specification for the use of other gangliosides or chemically modified gangliosides. However, the specification provides insufficient guidance of how to use derivatives of KLH as recited. Applicants assert that by routine experimentation one skilled in the art is enabled to make derivatives of KLH (see Applicants arguments on Paper No. 12; page 4). Applicants arguments are not persuasive.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). Rudinger et al. Teaches "particular amino acids and sequences for different aspects of biological activity can not be predicted a *priori* but must be determined from case to case by painstakingly experimental study" (see page 6). Salgaller et al teach modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. Fox et al. Teach methods for determining fragments which have antigenic activity is unpredictable. These references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and

fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-3, 6-12, 18-20, 44, and 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research) in view of Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663) and Ritter et al. (1990) for the reasons set forth in the Office Action mailed 6/10/96 (see Paper No. 9).

In response to Applicant's piecemeal analysis of the references (see Paper No. 11; pages 12-13; pages 7 and 8 of Paper No.12), one cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references. See MPEP 2145(d).

Applicants assert that the cited references (see Paper No. 11; page 11) do not suggest or motivate one of ordinary skill in the art to make the claimed invention. Applicants arguments are not persuasive for the reasons as set forth in the last Office Action (see Paper No. 9; page 8).

Applicants appear to argue that the rejection should be withdrawn since from the prior art (e.g. Ritter et al.) does not suggest or provide an expectation that the oligosaccharide portion of ganglioside conjugate remains intact or needs to be intact. Applicants arguments are not persuasive to obviate the rejection since applicants arguments are not commensurate in scope with the claimed invention. The claimed invention does not set forth that the oligosaccharide portion remains intact. Beyond this while Rutter et al. (1991) may not characterize that the

oligosaccharide portion remains intact with conjugation as asserted by applicants it would have been reasonable to expect the conjugate of the prior art would have the same properties of the conjugate as claimed since conjugating the KLH to a ganglioside as set forth by Ritter et al and as recited enhances the antibody response.

Applicants argue that the rejection should be withdrawn since the prior art does not teach of the requirement (e.g. need) for an adjuvant. Applicants argument is not persuasive since Livingston et al sets forth the vaccine administered to melanoma patient contains an adjuvant.

For the reasons set forth above and in the last Office Action said rejection is maintained.

11. Claims 4, and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research) in view of Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663) and Ritter et al. (1990) as applied to claims 1-3, 6-12, 18-20, 44, and 48-52 above and further in view of Kensil et al and Marciani et al. for the reasons set forth in the Office Action mailed 6/10/96 (see Paper No. 9).

Applicants appear to argue (see Paper No. 12-page 9; and Paper No. 11-pages 13-15) the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to claims 1-3, 6-12, 18-20, 44, and 48-52 above. For the reasons set forth above applicants arguments are not persuasive.

Applicants assert that Kensil et al and Marciani et al. do not suggest or motivate one of ordinary skill in the art to make the claimed invention. Applicants arguments are not persuasive for the reasons as set forth in the last Office Action (see Paper No. 9; pages 8 and 9).

12. Claims 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research) in view of Ritter et al., Livingston et al. (U.S. Patent No. 5,102,663) and Ritter et al. (1990) as applied to claims 1-3, 6-12, 18-20, 44, and 48-52 above and further in view of Irie et al. for the reasons set forth in the Office Action mailed 6/10/96 (see Paper No. 9).

Applicants appear to argue (see Paper No. 12-pages 10 and 11) the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to claims 1-3, 6-12, 18-20, 44, and 48-52 above. For the reasons set forth above applicants arguments are not persuasive.

Applicants argument that the teaching that GM2 is found on melanomas and breast carcinomas (see Paper No. 11-page 16) by Irie et al. does not provide sufficient motivation for one of ordinary skill in the art to practice the claimed invention is not persuasive. Since Livingston et al. teaches of a vaccine for melanoma patients which stimulates the production of anti-GM2 antibodies and GM2 is associated with a variety of tumors (i.e. melanoma and breast) as taught by Irie et al. one of ordinary skill in the art would have been motivated to use the vaccine composition not only melanomas as set forth by Livingston but also breast carcinomas since both types of tumors have GM2 present. For the reasons set forth above and in the last Office Action said rejection is maintained.

13. Any inquiry concerning this communication should be directed to Dr. Anthony C. Caputa, whose telephone number is 703-308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is 703-308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-308-4242.

Anthony C. Caputa, Ph.D.
July 6, 1997

ANTHONY C. CAPUTA
PRIMARY EXAMINER
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